Anal. Calcd for $C_{16}H_{15}O_7Cl \cdot 2H_2O$ (390.77): C, 49.17; 4.90; Cl, 9.07; H_2O; 9.2. Found: C, 49.81; H, 3.97; Cl, 9.78; H_2O; 7.6.

3′-Hydroxygriseofulvic Acid 7 from the Hydrolysis of 6.—Half of a solution of 14 mg of 6 in 0.3 ml of commercial grade spectro quality dioxane and 0.5 ml of 1 N HCl was heated on the steam bath in an open test tube for 15 min and water was added. The gum which separated, rapidly solidified. The light yellow solid was collected and washed well with water. It was soluble in aqueous bicarbonate and showed an infrared spectrum which was essentially identical with that of 3′-hydroxygriseofulvic acid (6) obtained above from the hydrolysis of epoxygriseofulvin (4).

(The other half of the solution was kept at room temperature for 16 hr and then poured into water. The solid which separated showed a tlc and infrared spectrum identical with those of starting 6.)

Formation of 6 by Reductive Hydrolysis of 5′-Bromoepoxy-griseofulvin (9).—A suspension of 1.1 g (0.0025 mol) of 9 and 0.65 g (0.0025 mol) of triphenylphosphine in 20 ml 'of methanol was heated on the steam bath for 1 min during which time the system became homogeneous. After allowing it to cool for 5 min, the reaction mixture was poured into ice water and the organic product extracted with ether–methylene chloride. Drying and evaporating the organic extract left 1.49 g of a light yellow foam which showed one major new spot on tlc (PhH–EtOAc 1:1) corresponding in R_f to that of 6 prepared above. The product corresponding to this spot was separated by thick layer chromatography (of *ca.* a 300-mg sample) using PhH–EtOAc 1:1 for development and was identified as 6 by ir, nmr, and mass spectral comparisons.

Registry No.—2, 25966-68-1; 5, 25966-69-2; 5a, 25966-70-5; 6, 26039-32-7; 7, 25966-71-6; 9, 25966-72-7.

Action of *N*-Halosuccinimide on 8-Quinolinol[1]

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A reinvestigation of the action of *N*-halosuccinimide on bis(8-quinolinolato)copper(II) revealed that, on monochlorination, a mixture of 5- and 7-chloro chelates resulted. On monobromination, only the 5-bromo chelate formed, and on monoiodination, the 7-iodo chelate was obtained.[2] This was in disagreement with the results of Prasad, *et al.*,[3] who reported that on monohalogenation of the same chelate with *N*-halosuccinimide, substitution took place exclusively in the 5 position. On the basis of dihalogenation studies of metal chelates with elemental chlorine and bromine and a list of reactivities of free and coordinated ligands found in the literature, Maguire and Jones[4] concluded that, with

the exception of tropolone, there are no authenticated instances where coordination changes the reactive position of an aromatic ligand toward electrophilic reagents. Hix and Jones[5] attempted to further strengthen this view by citing 109 reactions tabulated by Blatt[6] and 73 additional reactions listed by Berliner[7] where coordination does not affect orientation. Competitive bromination studies of mixtures of 8-quinolinol and its chelates with iron(III), chromium(III), and cobalt-(III) using insufficient bromine indicated that the rate of bromination of the chelates was about 35 times as rapid as that of the free ligands.

The present work was undertaken to further study what appeared to be the anomalous orientation of halogen when bis(8-quinolinolato)copper(II) was treated with *N*-halosuccinimide.[2] It was also of interest to reexamine the concept that chelation does not affect orientation of substituents in electrophilic substitution of aromatic ligands.

To approach the first problem, 8-quinolinol was reacted with *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), and *N*-iodosuccinimide (NIS) in chloroform, and the molar ratios of halogenating agent to substrate were 1:1, 2:1, and 3:1. The reaction time was 3 hr and two reaction temperatures were employed, ambient and 40–60°. The rationale for this approach and the identification and quantitation of the products were previously discussed.[2]

Table I contains the results obtained from the halogenation of 8-quinolinol with *N*-halosuccinimide. It

TABLE I

ACTION OF *N*-HALOSUCCINIMIDE ON
8-QUINOLINOL IN CHLOROFORM

Halogenating agent NCS[a]	Molecular ratio of *N*-halosuccinimide to 8-quinolinol	Temp, °C	Ox[b]	Products, % 5-ClOx	7-ClOx	5,7-Cl₂Ox
	1	ambient	95	1	4	0
	2	ambient	94	1	5	0
	3	ambient	94	1	5	0
	1	40–60	82	3	15	Tr[c]
	2	40–60	81	4	15	Tr
	3	40–60	77	6	17	Tr
NBS			Ox	5-BrOx	7-BrOx	5,7-Br₂Ox
	1	ambient	16	14	50	20
	2	ambient	0	0	0	100
	3	ambient	0	0	0	100
	1	40–60	14	12	58	16
	2	40–60	0	Tr	Tr	99
	3	40–60	0	0	0	100
NIS			Ox	5-IOx	7-IOx	5,7-I₂Ox
	1	ambient	Tr	94	Tr	5
	2	ambient	Tr	7	Tr	92
	3	ambient	0	Tr	0	99
	1	40–60	12	77	0	11
	2	40–60	Tr	10	0	90
	3	40–60	0	Tr	0	99

[a] NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide. [b] Ox = 8-quinolinol. [c] Tr = trace (<1%).

(1) This work was supported in part by the U. S. Public Health Service Grant No. AI-05808.

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(3) R. Prasad, H. L. D. Coffer, Q. Fernando, and H. Freiser, *ibid.*, **30**, 1251 (1965).

(4) K. D. Maguire and M. M. Jones, *J. Amer. Chem. Soc.*, **84**, 2316 (1962).

(5) J. E. Hix, Jr., and M. M. Jones, *J. Inorg. Nucl. Chem.*, **26**, 781 (1964).

(6) A. H. Blatt, *Org. React.*, **1**, 342 (1942).

(7) E. Berliner, *ibid.*, **5**, 229 (1949).

can be seen that the rate[8] of chlorination with NCS is very slow. The products formed were 5-chloro-, 7-chloro-, and a trace of 5,7-dichloro-8-quinolinol, and the orientation of the chlorine atom favored the 7 position over the 5 position by a ratio of about 4:1. The concentration of halogenating agent did not appear to affect the rate of reaction, but raising the temperature from ambient to 40–60° caused about a threefold increase in rate of chlorination. Bromination with NBS yielded three products in significant quantities, 5-bromo-, 7-bromo-, and 5,7-dibromo-8-quinolinol. The rate of bromination appeared to be rapid, as evidenced by no apparent effect due to temperature change, and on increasing the ratios of halogenating agent to 8-quinolinol, only the dibromo derivative was formed. The formation of 7-bromo-8-quinolinol was about four times that of the 5-bromo analog. The bromination of 8-quinolinol in the 7 position by *N*-bromo compounds has also been observed by Pearson, *et al.*,[9] and reexamined by Gershon, *et al.*[2] Iodination of 8-quinolinol with NIS yielded essentially two iodination products. 5-Iodo-8-quinolinol was the major product and 5,7-diiodo-8-quinolinol was formed in minor quantities. An increase in reaction temperature increased the rate of iodination of 5-iodo-8-quinolinol to yield a greater proportion of the 5,7-diiodo derivative than obtained at ambient temperatures.

A comparison of these results with the data previously reported on the halogenation of bis(8-quinolinolato)copper(II) with *N*-halosuccinimides[2] shows that, on chlorination of 1 equiv of ligand with 1 equiv of NCS, a high per cent of chelate was chlorinated, whereas very little free ligand was chlorinated. These results are in agreement with the conclusion of Hix and Jones,[5] that chelation with metals increases the rate of halogenation of 8-quinolinol. Comparable halogenations with NBS and NIS were not amenable to drawing conclusions as to the effect of chelation on rate of halogenation.

The orientation of the substituents of the monohalogenated products of the free ligand as compared with the chelate was unexpected. The chlorination products of 8-quinolinol consisted of about four times as much 7-chloro-8-quinolinol as 5-chloro isomer, and, on chlorination of the copper(II) chelate of 8-quinolinol, 5- and 7-chloro-8-quinolinols formed in about equal yield. The monobromination products of the free ligand consisted of 7-bromo and 5-bromo-8-quinolinols, also in the ratio of 4:1, but monobromination of the chelate yielded 80% 5-bromo-8-quinolinol and no detectable 7 isomer. The monoiodination products of the free ligand yielded 94% 5-iodo-8-quinolinol, whereas the chelate yielded 90% 7-iodo-8-quinolinol and 10% 5-iodo analog.[10] This is consistent with the hypothesis of Maguire and Jones[4] and Hix and Jones[5] that chelation

(8) The term "rate" is used in the sense of percent halogenated 8-quinolinol formed during the 3-hr reaction time.

(9) D. E. Pearson, R. D. Wysong, and C. V. Breder, *J. Org. Chem.*, **32**, 2358 (1967).

(10) It should be noted that our previous report[2] indicated that 99% 7-iodo-8-quinolinol was formed on iodination of bis(8-quinolinolato)copper-(II) with NIS. That assay was obtained by gas chromatography using a 5% QF-1 column. Later work showed that mixtures composed of 10% or less of one of the monoiode-8-quinolinols in the presence of 90% of the other could not be resolved even though mixtures of more nearly equal proportion could be assayed. The ir spectra of mixtures, composed of overwhelming proportions of one isomer, masked the presence of the other. The present work was carried out with a 1% Apiezon L column which can resolve mixtures of 5- and 7-iodo-8-quinolinols in all proportions.

of a ligand with a metal does not change the reactive positions of an aromatic compound toward electrophilic substitution. However, it is obvious that chelation does affect orientation of substituents in electrophilic substitution with *N*-halosuccinimide.

Halogenation of 8-Quinolinol with *N*-Halosuccinimides.—To a solution of 1 mmol of 8-quinolinol in 10 ml of chloroform was added 1, 2, or 3 mmol of the respective *N*-halosuccinimide. The mixture was stirred on a magnetic stirrer hot plate for 3 hr keeping the volume nearly constant by addition of chloroform, as needed. The hot plate was set to maintain temperatures of 40–60°. At the end of the reaction period, the solution was washed with three 5-ml portions of an aqueous solution containing 5% NaOAc and 5% NaHSO₃ in order to destroy unused *N*-halosuccinimide and to remove the succinimide formed. A portion of the chloroform solution was evaporated under a stream of air, and the residue was dissolved in acetonitrile. The quinolinols were converted to the trimethylsilyl derivatives by means of *N,O*-bis(trimethylsilyl)acetamide by the method of Klebe, *et al.*,[12] and chromatographed.

Registry No.—8-Quinolinol, 148-24-3; NCS, 128-09-6; NBS, 128-08-5; NIS, 516-12-1.

(11) Gas chromatography was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector to which was attached a Varian Aerograph Model 20 recorder. The column and conditions employed for the gas chromatographic separation of the chloro- and bromo-8-quinolinols were previously described.[2] To assay the iodo-8-quinolinols, a stainless steel column, 5 ft × 0.125 in. o.d., was packed with 1% Apiezon L coated on 80–100 mesh acid washed Chromosorb W, previously treated with dimethyldichlorosilane. The instrument was operated at a column starting temperature of 150° which was programmed at 6°/min to 250°. The injector and detector temperatures were maintained at 200 and 250°, respectively, while the flow rate of nitrogen was 22 ml/min. Retention times for 8-quinolinol and the 5-iodo, 7-iodo, and 5,7-diiodo derivatives were 1.7, 5.8, 6.2, and 11.8 min, respectively.

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The Reaction of Indole with *N*-Chloropyrrolidine and *N*-Chlorodibutylamine[1]

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Evidence is accumulating from recent developments in the chemistry of haloamines[2] which indicates that their reactions with organic substrates involve the intermediacy of electrophilic nitrogen species in either free-radical[3,4] or ionic[5] mechanisms. On this basis we have studied the reaction of indole with *N*-chloropyrrolidine (1) and *N*-chlorodibutylamine (2) with the hope that attack by electrophilic nitrogen intermediates would yield 3-aminoindole derivatives. Our results

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(1) Support from the Department of University Affairs, Province of Ontario, is gratefully acknowledged.

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